REMARKS/ARGUMENTS

Claims 107, 154, 163, 170, 178, 197, 190, 201, 206, 216, 217, 220 and 222 are currently amended; claims 110-112, 114, 157-161, 166-169, 173-177, 180-183, 193-196, 199, 200, 204, 205, 209-211, 218, 219, 221 and 223-229 were previously presented; and claims 1-106, 108, 109, 113, 115-153, 155, 156, 162, 164, 165, 171, 172, 179, 184-189, 191, 192, 198, 202, 203, 207, 208 and 212-215 are canceled without prejudice or disclaimer. It is submitted that no new matter has been added by virtue of the amended claims, which are supported by the claims and the disclosure of the application as originally filed.

Accordingly, the currently pending claims are now claims 107, 110-112, 114, 154, 157-161, 163, 166-170, 173-178, 180-183, 190, 193-197, 199-201, 204-206, 209-211 and 216-229.

Support for the Amended Claims

The amendments to claims 154, 163, 170, 178 and 217 are for the purpose of clarity and relate to form and/or grammar only. Claims 220 and 222 are rewritten in independent form.

Support for amended claims 107 and 216 may be found throughout the specification, including for example, on page 29, lines 12-23. Support for amended claims 190, 197, 201, and 206 may be found throughout the specification, including for example, on page 16, lines 11-14.

Priority

Applicants have amended the specification to update the status of the prior application. The specification now recites that this application "is a continuation-in-part of patent application Serial No. 09/302,896, filed April 30, 1999, now U.S. Patent No. 6,866,842, issued March 15, 2005. The application also specifies that the contents of the cited document are incorporated by reference (page 51, lines 8-10 of the original specification). Accordingly, Applicants submit that the application now formally complies with conditions for receiving the benefit of an earlier priority date under 35 U.S.C. §120.

Specification

The Examiner objected to the disclosure of the application because the status of U.S. patent application 09/302,896 listed in the specification needs updating. Applicants have amended the specification to update the status of patent application U.S. Serial No. 09/302,896 to reflect that is it now issued U.S. Patent No. 6,866,842. Accordingly, Applicants request that this objection be withdrawn.

Objections to the claims

The Examiner objected to claims 220 and 222 as being dependent upon a rejected base claim. The Examiner indicated that claims 220 and 222 would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims. In view of the current amendments to claims 220 and 222, it is respectfully submitted that these claims should be deemed allowable.

The claims fulfill the requirements of 35 U.S.C. §112, first paragraph

Claims 107-112, 114, 154, 157-161, 163, 166-170, 173-178, 180-183, 185, 216-218, and 223-229 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, the broadening limitation "(b) replating non-adherent cells from step (a) in a second collagen-coated container" is allegedly not supported by the as-filed specification. Applicants respectfully disagree with the Examiner's assertion.

Applicants submit that claims 107, 154, 163, 170, 178, 216, 217, and the claims depending from these claims, comply with the written description requirement and are fully supported by the instant specification. For example, at page 29 lines 12-23 of the specification, Applicants broadly describe re-plating of non-adherent cells from one collagen-coated container into a second collagen-coated container. By way of example, the specification describes a procedure in which, preferably after 30-40% of the cells from the original cell suspension adhered to the container, the supernatant containing non-adherent cells from the first container may be removed from the container (e.g., flask) and re-plated into a fresh container. (See, Example 1).

Moreover, the specification incorporates by reference two priority documents (i.e., U.S. Serial Nos. 60/083,917 and 09/302,896), which broadly describe re-plating non-adherent cells from one collagen-coated container to a second collagen-coated container. See, for example, Example 1 of the U.S. Serial No. 09/302,896. An example is also provided in which cells are re-plated after 15-20% of the cells from the original cell suspension adhered to the container. (See, U.S. Serial No. 09/302,896, page 81, Example 11). Therefore, Applicants submit that 30-40% cell adherence is not a required or essential element of the invention, and the broadening limitation "(b) replating non-adherent cells from step (a) in a second collagen-coated container" is supported by the as-filed and related specifications. Further, one of ordinary skill in the art reading the as-filed and related applications would understand that, at the time of filing the application, Applicants were in possession of the invention as defined by claims 107-112, 114, 154, 157-161, 163, 166-170, 173-178, 180-183, 185, 216-218, and 223-229. Thus, withdrawal of this rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. §112, second paragraph

Claims 154, 157-161, 163, 166-170, 173-178, 180-183, 185, 217, 223-226 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner stated that claims 154, 163, 170, 178, and 217 have insufficient antecedent basis for reciting "re-plating non-adherent cells from step (a)" in step (ii).

Applicants have amended claims 154, 163, 170, 178, and 217 to recite "re-plating non-adherent cells from step (i)" in step (ii). In view of this amendment, it is respectfully submitted that the rejection of independent claims 154, 163, 170, 178 and 217 and claims depending from these claims is moot.

In addition, the Examiner stated that claims 154, 163, 170, 178, and 217 have insufficient antecedent basis for reciting "re-plating non-adherent cells from step (b)" in step (iii). Applicants have amended claims 154, 163, 170, 178, and 217 to recite "re-plating non-adherent cells from step (ii)" in step (iii). In view of this amendment, the rejection of independent claims 154, 163, 170, 178 and 217 and claims depending from these claims is moot. Withdrawal of the rejection is thus respectfully requested.

The claims satisfy the requirements of 35 U.S.C. § 102

The Examiner rejected claims 107, 114, 216, and 218 under 35 U.S.C. § 102(b) as allegedly being anticipated by the publication of Rando et al. (hereinafter "Rando"). Specifically, the Examiner asserted that Rando teaches a method of isolating myoblasts using the same method steps as recited in instant claims 107 and 216.

Applicants respectfully disagree with this rejection and traverse as follows:

It is well established that a claim is anticipated only if each and every element set forth in the claim is found in the cited reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §2131. Thus, "[t]he identical invention must be shown in as complete detail as contained in the patent claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); cited by MPEP §2131.

Rando does not teach each and every element of Applicants' method of isolating an end population of muscle-derived progenitor cells, as defined by independent claims 107 and 216. Although Rando teaches enriching myoblasts in primary cultures by a preplating method with reference to Richler and Yaffe (Richer and Yaffe, 1970, *Developmental Biology*, 23:1-22), the method of Rando differs from Applicants' method. For example, Rando's method involves distributing a muscle cell suspension into untreated tissue culture dishes and after 40-60 minutes aspirating the medium and seeding cells into culture plates containing growth medium as described by Rando. (p. 1277). Rando's cultured cells are maintained in selective growth conditions and are passaged over time, e.g., two weeks, as taught by Rando. (p. 1278, Figure 1 legend).

Rando does not teach Applicants' method which involves isolating muscle-derived progenitor cells by repeated re-plating of non-adherent cells in new collagen-coated containers at least three times. Unlike Rando, Applicants' method includes the re-plating steps as specified and results in an end population of muscle derived progenitor cells having the properties and characteristics described by Applicants.

In fact, Rando can be considered to teach away from Applicants' method by referencing the method of Richler and Yaffe in connection with Rando's method. Richler and

Yaffe teach that in their attempts to establish myogenic cell lines, "... after 3-5 passages cell multiplication ceased entirely and the line was lost." (Richler and Yaffe, page 4, Experimental). By contrast and in accordance with the presently claimed invention, Applicants require that the muscle-derived cells be re-plated at least three times, which results in an end population of viable, non-fibroblast, desmin-expressing MDCs.

Because Rando does not teach each and every element of Applicants' presently claimed invention, Rando does not anticipate the present claims. Accordingly, Applicants respectfully request that the rejection of claims 107, 114, 216, and 218 be withdrawn.

The claims satisfy the requirements of 35 U.S.C. § 103

Claims 190, 193, 194, 196, 197, 199, 201, 204, 206, 209-210, 227, and 228 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,667,778 to Atala (hereinafter "Atala") taken with U.S. Patent No. 6,261,832 to Law (hereinafter "Law"). The Examiner has also rejected claims 190, 193-197, 199-201, 204-206, and 209-211 as allegedly being unpatentable over Atala taken with Law, and further in view of U.S. Patent No. 5,206,028 to Li (hereinafter "Li").

It is well understood that the presently claimed invention must be considered as a whole in determining differences between the prior art and the presently claimed invention. M.P.E.P. §2141.02. In addition, all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. Additionally, it is established that a reference must be considered for all that it teaches, i.e., as a whole and in its entirety. This includes a consideration of portions that would lead away from the claimed invention. *W L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.Cir. 1983), as cited in the MPEP §2141.02. Specific sentences should not be taken out of context from prior art references; all of the teachings of the reference must be considered to determine what the reference really teaches. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). Furthermore, combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. *ACS Hospital Systems, Inc. v. Montifiore Hospital,* 221 USPQ 929, 993 (Fed. Cir. 1984). Absent some teaching, suggestion, or incentive supporting the combination,

obviousness cannot be established by combining the teachings of the prior art. *In re Geiger*, 815 F.2d 686, 688 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

As the Examiner admits at page 7, line 11-12 of the 07/25/05 Office Action, Atala does not teach using skeletal muscle cells in the method of treating conditions involving gastrointestinal tract and urinary tract. The Examiner also states that Law teaches a method of augmenting tissue or organ using myogenic cells. The Examiner further opines that it would have been obvious to use skeletal myogenic cells of Law in Atala's method of augmenting or bulking bladder or sphincter. Applicants respectfully disagree with the Examiner.

As amended, claims 190, 197, 201, and 206, and all of the claims depending therefrom, require that Applicants' isolated, desmin-expressing, skeletal muscle-derived progenitor cells, or a clonal population thereof, survive over time in esophageal, sphincter, bladder muscle tissue and in skin tissue to provide augmented or bulked esophageal, sphincter, bladder muscle tissue and skin tissue in a recipient.

Applicants submit that the Examiner's §103 rejection is not appropriate because Atala, if properly combined with Law, does not teach or suggest all of the limitations of Applicants' present claims. Neither of the cited references teaches a method of augmenting or bulking smooth muscle tissue, such as esophageal, sphincter and bladder muscle tissue, and skin tissue, by introducing a composition comprising skeletal muscle-derived progenitor cells into these types of smooth muscle tissue areas, wherein the isolated, desmin-expressing, skeletal muscle-derived progenitor cells, or a clonal population thereof, survive over time in these areas of physiologically different muscle tissue to provide augmented or bulked smooth muscle and skin tissue in a recipient.

Rather, Atala teaches a method of treating vesicourethral reflux, incontinence and other smooth muscle defects by injecting cells of the same origin and physiological characteristics, i.e., smooth muscle cells, mixed with a polymeric material, into an area of a smooth muscle defect. Law teaches and exemplifies a method of treating a hereditary and degenerative muscle disorder using skeletal myoblasts injected into sites of skeletal muscle. Nothing is taught or suggested in the combination of the two cited references regarding augmenting or bulking the smooth muscle types with skeletal muscle-derived progenitor cells as taught and

specified by Applicants. In addition, nothing is taught or suggested in the combination of the two cited references regarding treating Applicants' specified smooth muscle-related conditions using skeletal muscle-derived cells that are able to survive after transplantation in a physiologically different tissue type.

More particularly, Atala teaches the use of bladder muscle cells embedded in biodegradable polymer, to treat bladder-related defects, such as vesicoureteral reflux, incontinence and other defects. (Atala, Col. 4, lines 40-59; Col. 4, lines 65-67 to Col. 5, lines 1-7; and Col. 5, lines 25-35). In fact, Atala teaches away from the Applicants' presently claimed invention by explicitly disclosing that "passaging [of cells is] necessary to remove contaminating non-bladder muscle cells." (Atala, Col. 5, lines 35-37).

Applicants have previously pointed out in their March 17, 2005 Amendment and Response the significant differences between smooth muscle cells and skeletal muscle cells, as is known and appreciated by those having skill in the pertinent art. For example, smooth muscle cell are vastly different from the skeletal muscle cells when their physiology, function, mechanism of contraction, and other characteristics are compared.

Considering the teaching of Atala to use only bladder smooth muscle cells to treat only smooth muscle disorders in related smooth muscle areas, in conjunction with a knowledge of the clear-cut physiological differences between smooth muscle cells and tissues and skeletal muscle cells and tissues, it would not have been obvious to one of skill in the art to use a cell type other than Atala's disclosed bladder smooth muscle cells to treat the smooth muscle disorders described by Atala and Atala's method.

In particular, based on the teachings of Atala and knowledge in the art concerning smooth and skeletal muscle cell/tissue differences, it would not have been obvious to one having skill in the art at the time to use skeletal myoblasts as described by Law to treat a smooth muscle disorder such as vesicoureteral reflux, incontinence, or a bladder defect. Law is concerned with the use of skeletal muscle cells to treat skeletal muscle related disorders, such as muscular dystrophy. That one would not be led to use non-bladder, e.g., skeletal muscle, cells to treat the conditions of Atala's invention is especially true given Atala's teaching that non-bladder muscle cells are considered to be contaminants and are removed

prior to practicing Atala's method of treating smooth muscle/bladder-related conditions with smooth muscle cells.

Additionally, Applicants submit and the Examiner has noted that neither Atala nor Law addresses each and every embodiment for using a collagen sponge material as the carrier in the methods [claimed by Applicants.] (07/25/05 Office Action, page 11, 2nd paragraph). The Examiner remarks that Li teaches collagen membranes having physical and biological properties and opines that it would have been obvious to combine the teachings of Atala and Law in further view of Li to use the collagen sponge material in the method of augmenting or bulking muscle tissue. Applicants respectfully disagree.

In fact, Li teaches a dense collagen membrane matrix material and method of making such material. Li fails to teach, and does not suggest using, the described and contemplated collagen matrix material in methods of augmenting or bulking smooth muscle tissue, such as esophageal muscle tissue, sphincter muscle tissue, or skin tissue, by injecting into this smooth muscle tissue or skin tissue isolated skeletal muscle-derived progenitor cells as described in Applicants' claims, namely, claims 190, 197, 201, and 206. Further, Li does not teach, suggest, or contemplate that isolated skeletal muscle derived cells will survive and augment or bulk the smooth muscle or skin tissue after injection with a collagen sponge material as carrier.

Li's teaching does not compensate for the above-described deficiencies of Atala and Law, both alone and in combination. Combining Atala and Law in consideration of the complete teachings of Li would not lead one having skill in the art to arrive at Applicants' presently claimed invention for the reasons detailed above. Because a proper combination of Atala and Law, in further consideration of Li, does not encourage or prompt one having skill in the art to make the modifications that are necessary to achieve Applicants' presently claimed invention, these cited references, absent some teaching, incentive, or suggestion to support the combination, do not make obvious Applicants' claimed methods.

Without Applicants' own teaching and invention, as defined by the present claims, one having skill in the art, considering the significant physiological distinctions between smooth and skeletal muscle cells and tissues, would not be motivated to use skeletal muscle-derived cells to augment or bulk smooth muscle tissues of specific types, or to include a collagen

carrier material with the skeletal muscle cells, for augmenting or bulking Applicants' described types of smooth muscle tissue. Without the proper motivation, in conjunction with the failure of the cited art to teach or suggest using skeletal muscle cells to augment or bulk specific smooth muscle tissues, the cited combination of Atala, Law and Li, considered in their entireties, does not make obvious Applicants' invention as presently claimed.

For at least these reasons, it is respectfully requested that the § 103 rejections be reconsidered and withdrawn.

Double Patenting

Claims 107, 216, 219, and 221 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 260, 266, 267, 273, 274, and 280, i.e., claims 1, 7, 8, 14, 15 and 21, of U.S. Patent No. 6,866,842. According to the Examiner, the conflicting claims are not identical, but are considered to be not patentably distinct from each other because the instant claims and the claims of the '842 patent are directed to using the same method of isolating muscle derived progenitor cells and a method of augmenting or bulking muscle tissue in the bladder muscle tissue using muscle derived progenitor cells.

To expedite the prosecution of the instant application without acquiescing to the propriety of this rejection, Applicants submit herewith an executed terminal disclaimer and the required fee. Accordingly, withdrawal of the rejection is respectfully requested.

Common Ownership of the presently claimed invention and the invention claimed in U.S. Patent No. 6,866,842

The Examiner has provided further remarks regarding an alleged lack of a patentable distinction between the invention claimed in claims 107, 216, 219 and 221 of the instant application and the invention claimed in claims 260, 266, 267, 273, 274 and 280 (i.e., claims 1, 7, 8, 14, 15 and 21) of issued patent, U.S. Patent No. 6, 866,842. The issue raised by the Examiner is resolved since the inventions described in the instant application and those described in U.S. Patent No. 6,866,842 were commonly owned, or were under obligation to be

commonly assigned, by the University of Pittsburgh at the time the present invention was made.

To support the common ownership, Applicants provide copies of the recorded Assignments of the instant application and U.S. Patent No. 6,866,842. In addition, a statement of common ownership is separately set forth hereinbelow.

Accordingly, the common ownership of the claimed inventions precludes a potential rejection under 35 U.S.C. §103 (§103(a)) as mentioned by the Examiner. (07/25/05 Office Action, page 14).

STATEMENT OF COMMON OWNERSHIP UNDER 35 U.S.C. §103

Applicants hereby submit that the subject application and U.S. Patent No. 6,866,842 were, at the time the invention of the instant application was made, owned by, or subject to an obligation of assignment to, the University of Pittsburgh. Copies of the assignment information for U.S. Patent No. 6,866,842 and the instant application are attached hereto.

This statement and accompanying attachments are considered to be sufficient evidence for establishing common ownership under 35 U.S.C. §103 for the instant application and U.S. Patent No. 6,866,842 by the University of Pittsburgh at the time the invention was made. *See* MPEP §706.02(1)(2)(I and II) and 1241 O.G. 96 (December 26, 2000).

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this amendment and response, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**, Reference no. **28682-501-CIP,** Customer Number: **35437**.

Should an extension of time be required for the timely consideration of this Amendment and response, the Commissioner is hereby authorized to grant any such extension of time as may be necessary, and to charge any additional fee(s) owed by Applicants for such extension of time, to the above-mentioned Deposit Account, Reference and Customer Numbers.

If the Examiner believes that it would be helpful to discuss the application to advance the prosecution of the application and claims to allowance, he is respectfully requested to telephone applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in this effort.

Respectfully submitted,

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